Remarks

Claim 36 was amended to delete knots, twists, braids, and coils.

Claim 46 was amended to specify that the seeds or spacers are located at varying distances.

Claim 58 was amended to correct the dependency.

Claim 60 was amended to more clearly define the seed.

Claims 61-63 were amended to specify that the seeds are administered at designated intervals. Support for the amendment is found at least in claims 61-63.

Claims 67-70 were amended to specify that the one or more structures prevent migration or maintain orientation. Support for the amendment is found at least in claim 36.

New claims 71-79 were added. Support for new claim 71 is found at least in paragraphs 0087, 0088, and 0094 of the published application. Support for new claims 72 and 73 is found at least in the Figures as originally filed. Support for new claims 75-78 is found at least in Figure 6 and paragraphs 0105 and 0116 of the published application. Support for new claim 79 is found at least in claims 50 and 51.

In the event this Amendment and Response does not place the application in condition for allowance, the undersigned requests an interview with the Examiner, his Supervisor, and a Quality Control Specialist.

Rejection Under 35 U.S.C. § 102

Claims 36-46, 48-50, 52-54, and 58 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,264,599 to Slater *et al.* ("Slater"). Applicant respectfully traverses this rejection.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 US 947 (1987); Scripps Clinic & Research Found v. Genentech Inc., 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in Scripps, 18 USPQ2d at 1010:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation.

Analysis

Slater

Slater describes a radioactive seed having a means for engaging the tissue surrounding the seed (col. 3, lines 23-25). The means for engaging the tissue are three spring elements which

are biased away from the seed capsule (col. 3, lines 53-55). Slater does not disclose or suggest a seed comprising one or more biodegradable structures that prevent migration and/or maintain orientation as required by claims 36 and the claims dependent thereon. The only mention of bioabsorbale polymers is with respect to the spacing links which can be used to link the seeds described in Slater to form a strand (col. 7, lines 12-16). Spacing links are not therapeutic seeds.

Slater also describes an engagement means formed of a hydrophobic material, e.g., urethane or other expandable plastic material which cause a ring to enlarge when exposed to moisture within the body (col. 6, lines 33-40). Again, Slater does not disclose or suggest biodegradable materials for forming the ring.

Further, it is not clear how the ring of hydrophobic material would swell since hydrophobic materials repel water and thus do not swell in the presence of moisture since they do not absorb water. The disclosure in an allegedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003).

As discussed above, Slater fails to disclose how a hydrophobic material swells in the presence of moisture. Even if one could argue that such materials swell, in order to prevent the seed from migrating back down the needle track, the ring would have to swell in the applicator in order to create resistance to the suction from the vacuum created by withdrawing the

needle/obturator. This would require the ring to be exposed to moisture and swell prior to administration since the ring could not swell to a sufficient size to prevent movement in the time it takes to remove the needle after administration. Slater does not disclose or suggest how to pre-swell the ring prior to administration. Further, Pre-swelling the ring could make it more difficult to load the seeds into the obturator and/or the seeds could jam in the obturator. Slater does not teach one of skill in the art how to make and use a seed containing a ring of hydrophobic material without undue experimentation. Therefore, for at least the reasons discussed above, claim 36 is novel over Slater.

Further, Slater does not disclose or suggest the biodegradable structures listed in claim 36. Slater does not disclose each and every element of claims 36-46, 48-50, 52-54, and 58. Therefore, claims 36-46, 48-50, 52-54, and 58 are novel over Slater.

Claim 44, 46, 48, 52-54, and 58 are novel over Slater for the additional reasons provided below.

Slater does not disclose or suggest the seed of claim 41, wherein the color, texture, diameter, hardness, or shape of the spacers is used for identification and demarcation as required by claim 44. Therefore, claim 44 is novel over Slater.

Slater does not disclose or suggest the seed of claim 41, wherein the spacers are located at varying distances from one another, separated by one, two, three, four, five or more seeds or the seeds are located varying distances from one another, separated by one, two, three, four, five or more spacers, as required by claim 46. Therefore, claim 46 is novel over Slater.

Slater does not disclose or suggest the seed of claim 36, wherein the one or more biodegradable structures are formed from a smart polymer or shape memory polymer as required by claim 48. Therefore, claim 48 is novel over Slater.

Slater does not disclose or suggest the seed of claim 36, wherein the imaging, radiopaque, or diagnostic marker is the biocompatible carrier as required by claims 52-54. Further, Slater does not disclose or suggest the seed of claim 52, wherein the seed further comprises a means of tracing the radioactive contents, such as a luminescent, colored, pigmented, dyed, tagged, or quantum dot tracer as required by claims 53 and 54. Therefore, claims 52-54 are novel over Slater.

Slater does not disclose or suggest the seed of claim 36 comprising structures that adhere to tissue as required by claim 58. Slater does not mention the term "adhesion" anywhere in the specification. Therefore, claim 58 is novel over Slater.

New claims 71-79 are novel over Slater for at least the reasons discussed above.

Rejection Under 35 U.S.C. § 103

Claims 36-46 and 48-70 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Published Patent Application No. 2001/0044567 to Zamora *et al.* ("Zamora"), in view of Slater, U.S. Patent No. 6,251,135 to Stinson *et al.* ("Stinson"), and U.S. Published Patent Application No. 2002/0058854 to Reed *et al.* ("Reed"). Applicants respectfully traverse this rejection.

Legal Standard

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

Graham v. John Deere, 383 US 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). These four factors are traditionally referred to as the "Graham factors". The Graham factors were affirmed by the U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

Evidence of secondary considerations to be considered in an analysis under 35 U.S.C. § 103 include commercial success, long felt but unresolved needs, failure of others, etc. M.P.E.P § 2145, *citing* Graham, 383 U.S. at 17, 148 U.S. P.Q. at 467. Evidence may also include evidence that the claimed invention yields unexpectedly improved properties or that the claimed invention possesses unexpected properties. M.P.E.P § 2145, *citing In re Dillon*, 919 F.2d 688, 692-93, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990).

Analysis

Zamora in view Slater, Stinson, and Reed

(i) The Claimed Seeds

Independent claim 36 and the claims dependent therein a seed, for implantation into a subject, wherein the seed is a combination product comprising

a) a biocompatible carrier,

b) one or more therapeutic components,

c) an imaging, radiopaque, or other diagnostic marker, and

d) one or more structures to maintain location or orientation of the seed selected from the group consisting of one or more biodegradable structures effective to prevent migration upon implantation of the seed in tissue, one or more biodegradable structures effective to maintain orientation in tissue, and one or more compliant setal or hair structures which impart adhesive properties upon implantation into a target tissue.

The one or more biodegradable structures comprise studs, knobs, ribs, fins, grapple shaped anchors, wings, stabilizers, bristles, rings, bands, hooks, and combinations thereof. The seed has a size and shape suitable for passing through the bore of a needle or catheter having an interior diameter of less than about 2.7 mm (10 gauge).

Independent claim 60 and the claims dependent thereon, define a seed, for implantation into a subject, wherein the seed is a combination product comprising

a) a biocompatible carrier,

b) one or more therapeutic components,

c) an imaging, radiopaque, or other diagnostic marker, and

d) one or more structures to maintain location or orientation of the seed wherein the one or more biodegradable structure comprise one or more bands and one or more ribs or wings and

wherein the seed has a size and shape suitable for passing through the bore of a needle or catheter having an interior diameter of less than about 2.7 mm (10 gauge).

(ii) The Scope and Content of the Prior Art

Zamora

Zamora describes a bioabsorbable brachytherapy device containing a tubular housing with sealed ends and an enclosed radioactive material (abstract). The radioactive material includes a radioisotope, such as Pd-103 or I-125 (abstract). Specifically, Zamora discloses brachytherapy seeds made from a bioabsorbable polymer (paragraphs 32 and 58). Zamora discloses that the outer surface of the device has sufficient permanence or persistence so that the radioactive source material remains localized at the site of implantation (paragraph 0029). In other words, the outer surfaces of the device remains intact long enough for the radioactive material to remain within the walls of the seed. The seeds described in Zamora have a smooth surface (*see* Figure 7). Zamora teaches that seed migration can be minimized by preparing a seed whose density approximates the density of the tissue in which it is implanted. Zamora does not disclose or suggest a seed comprising one or more biodegradable structures that prevent

migration and/or maintain orientation of the seed, let alone the specific structures listed in claim 36.

Slater

Slater is discussed above. Slater does not disclose or suggest a seed comprising one or more biodegradable structures that prevent migration and/or maintain orientation as required by claims 36 and the claims dependent thereon let alone the specific structures specified in claim 36.

Stinson

Stinson describes retrievable radiopaque markers for use in implantable endoprostheses to improved radiopacity and locatability of endoprostheses in various medical procedures (col. 2, lines 6-9). Implantable endoprostheses include stents, stent-grafts, grafts, filters, occlusive devices, and valves (col. 5, lines 6-8). These devices are used to repair or support diseased or damaged arteries and body lumens (col. 1, lines 13 and 14). The marker can be threaded adjacent a helical strand in the implantable endoprosthesis, circumferentially around the implantable endoprosthesis, in a straight line in the axial direction of the implantable endoprosthesis, or disposing the wire in the form of pigtail-shaped rings, coils, or knots around filament crossing points in the implantable endoprosthesis (col. 2, lines 15-21). Stinson does not disclose or suggest seeds, let alone seeds that contain one or more biodegradable structures that protrude from the surface, to prevent migration and/or maintain orientation. Furthermore, an endoprosthesis is an artificial implant placed inside the body to replace a missing body part. A therapeutic seed introduced into soft tissue through the bore of a needle is not an endoprosthesis.

Reed

Reed describes a loader device for implanting seeds (paragraphs 0005-0013).

(iii) The Differences Between the Claimed Seeds and the Prior Art

Zamora in combination with Slater does not disclose or suggest one or more biodegradable structures that prevent migration and maintain orientation

Zamora is discussed above. Zamora does not disclose or suggest a seed comprising any surface structures, let alone one or more biodegradable structures that prevent migration and/or maintain orientation of the seed or the specific structures listed in claim 36.

Slater is discussed above. Slater describes seeds containing three spring elements which are biased away from the seed capsule or a ring made of a hydrophobic material, such as a urethane, that enlarges upon exposure to moisture. The only disclosure in Slater regarding the spring elements is that they are resilient and are shaped such that when the free ends are forced towards the second end of the capsule, the elements, along their length, contour to the exterior of the capsule (col. 5, lines 30-38). There is no disclosure in Slater regarding the types of materials used to make the spring elements, let alone a disclosure or suggestion of biodegradable materials. With respect to the ring, Slater discloses that the ring can be made of a hydrophobic material, such as a polyurethane or an expandable plastic. Slater does not disclose or suggest one or more **biodegradable** structures that prevent migration and/or maintain orientation. Therefore, Slater does not cure the deficiencies of Zamora.

Further, Slater provides no evidence that the spring elements or ring described therein prevent migration of the seeds. The structures in Slater must actively engage the surrounding tissue. Upon expulsion from the syringe, the spring like elements of Slater must bias away from the seed to engage the tissue. It is possible that pressure from the surrounding tissue forces the spring elements back against the capsule of the implanted seed or prevents the spring elements from employing at all, thereby preventing or inhibiting engagement with the surrounding tissue. In contrast, the one or more biodegradable structures in the claimed seeds passively engage tissue and thus pressure from the surrounding tissue actually increases engagement of the structures with the surrounding tissue.

With respect to the ring, Slater fails to teach one of ordinary skill how to make and use a seed containing a hydrophobic ring for at least the reasons discussed above with respect to the rejection under 35 U.S.C. §102 (e) over Slater.

The combination of Zamora and Slater is improper since such a combination would make Zamora inoperable for its intended purpose

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Zamora teaches the use of seeds which approximate the size and shape of current devices and provide optimal radiation dosimetry (paragraph 0032). The seeds described in Zamora are smooth in order to provide radially uniform dosimetry. Zamora discloses that seed migration can

be minimized by designing a seed whose density approximates the density of the tissue in which it is implanted (paragraph 0083). In contrast, Slater discloses incorporating spring elements or an expandable ring on a seed which result in radially non-uniform dosimetry (col. 3, lines 13-20). One of ordinary skill in the art would not be motivated to combine Zamora and Slater since the structures defined in Slater would make the seeds in Zamora inoperable for their intended purpose. Therefore, the combination of Zamora and Slater is improper.

Stinson describes a retrievable radiopaque marker for use in implantable endoprostheses to improve radiopacity. As discussed above, endoprostheses are not therapeutic seeds. Stinson is a non-analogous reference and therefore the combination of Zamora and Slater with Stinson is improper as noted in MPEP 2141.01(a).

Further, Stinson does not disclose or suggest one or more structures to prevent migration and/or maintain orientation. The passage cited by the Examiner regarding the ends of the marker, which can may be tied, twisted, knotted, welded, or adhesively connected together describes the means for attaching the retrievable marker to the endoprosthesis. The endoprosthesis can be modified to contain a hook, knob, or eyelet to which is tied or attached the radio marker to affix it to the endoprosthesis (col. 6, lines 8 and 9). Stinson discloses that the ends of the marker are manipulated to lie in ***an unobtrusive low-profile position*** (col. 15, lines 34-37). The marker is attached in such a way that it lies almost entirely within the plane of the device to which it is connected and therefore is not effective at preventing movement (col. 9, lines 1-3). This is particularly important in implants which are implanted within vessels, such as

stents or valves, since any protrusion from the surface could damage the wall of the vessel. Stinson does not disclose or suggest any role for radiopaque markers in the interface between the marked endoprosthesis and the body lumen in which the endoprosthesis resides much less biodegradable structures that interact with tissue prevent movement as required by the claims.

In fact, Stinson explicitly teaches away from structures that interact with tissue. Stinson teaches that the radiopaque marker does not interface with the tissue at the implantation site, as removing the radiopaque marker from the endoprosthesis can be done without impacting the body or vessel lumen (Figure 9). Therefore, the combination of the radiopaque marker of Stinson and the seed of Slater or Zamora would not result in a seed with biodegradable structures to prevent migration as required by the claims.

Stinson does not cure the deficiencies of Zamora and Slater for at least the reasons discussed above. Further, the Examiner has failed to provide an explanation of how one of ordinary skill in the art would combine Zamora, Slater, and Stinson to arrive at the claimed seeds. Therefore, the Examiner cannot argue that one of ordinary skill in the art would be motivated to combine the seeds of Zamora and Slater with the endoprosetheses of Stinson to arrive at the claimed seeds.

Reed is discussed above. Reed is concerned with devices for injecting seeds, not the seeds themselves. Reed does not cure the deficiencies of Zamora, Slater, and Stinson.

Accordingly, claims 36-46 and 48-76 are not obvious over Zamora in view of Slater, Stinson, and Reed.

Moreover, claims 44, 46, 48, 52-54, and 58 are not obvious over Zamora in view of Slater, Stinson, and Reed for the additional reasons provided below.

The references in combination do not disclose or suggest the seed of claim 41, wherein the color, texture, diameter, hardness, or shape of the spacers is used for identification and demarcation as required by claim 44. Therefore, claim 44 is not obvious over Zamora in view of Slater, Stinson, and Reed.

The references in combination do not disclose or suggest the seed of claim 41, wherein the spacers are located at varying distances from one another, separated by one, two, three, four, five or more seeds as required by claim 46. Therefore, claim 46 is not obvious over Zamora in view of Slater, Stinson, and Reed.

The references in combination do not disclose or suggest the seed of claim 36, wherein the one or more biodegradable structures are formed from a smart polymer or shape memory polymer as required by claim 48. Therefore, claim 48 is not obvious over Zamora in view of Slater, Stinson, and Reed.

The references in combination do not disclose or suggest the seed of claim 36, wherein the imaging, radiopaque, or diagnostic marker is the biocompatible carrier as required by claims 52-54. Further, the references in combination do not disclose or suggest the seed of claim 52, wherein the seed further comprises a means of tracing the radioactive contents, such as a luminescent, colored, pigmented, dyed, tagged, or quantum dot tracer as required by claims 53

and 54. Therefore, claims 52-54 is not obvious over Zamora in view of Slater, Stinson, and Reed.

The references in combination do not disclose or suggest the seed of claim 36 comprising structures that adhere to tissue as required by claim 58. Slater does not mention the term "adhesion" anywhere in the specification. Therefore, claim 58 is not obvious over Zamora in view of Slater, Stinson, and Reed.

The references in combination do not disclose or suggest a seed comprising the biodegradable structures specified in claim 60, 72, and 73. Therefore, claims 60, 72, and 73 are not obvious over Zamora in view of Slater, Stinson, and Reed.

New claims 71-79 are non-obvious over Zamora in view of Slater, Stinson, and Reed for at least the reasons discussed above.

Evidence of Secondary Indicia of Non-obviousness

Even if the examiner had found separate references identifying the claimed elements,, which he has not, Applicant has evidence of the type deemed by the U.S. Supreme Court sufficient to rebut an allegation of obviousness: long standing need and commercial success.

Long Standing Need

The problem with migration is a significant, and to date, unsolved problem in the field. This is clearly established by the references discussed in the Amendment and Response filed on March 9, 2009. Applicant has shown that up to the present time, seed migration is still a

significant problem, particularly in brachytherapy, and that the prior art seeds have failed to solve the problem of seed migration.

Commercial Success

Contrary to the Examiner's statement at page 12, lines 1-3 of the Office Action dated July 28, 2009 the Examiner is aware of the composition of AnchorSeed and has been since at least the interview between the Examiner and the undersigned on December 11, 2008. As discussed in the Amendment and Response filed on March 9, 2009 and shown in the enclosed picture from the AnchorSeed website and the enclosed article by Badwan *et al.*, AnchorSeed contains four rings around the circumference of the seed, one at each end cap of the seed and two smaller medial rings. The rings are connected by two longitudinal ribs that run opposite each other along the lateral surface of the seed and connect the two end caps or rings. The biodegradable elements are made from polyglycolic acid (PGA). The incorporation of the rings and the rib results in a seed having a diameter 30% greater than standard seeds. The larger seed dimensions fill the needle track more completely than standard seeds, thereby minimizing draw back when administered into the tissue. Drawback is a frequent adverse event associated with standard seeds. Such a seed is within the scope of the claims and the Examiner has failed to show otherwise.

As discussed in the Amendment and Response, the Anchorseed went on sale in March 2008. There has generally been a steady increase in the number of patients treated with Anchoseed, with 57 treated in October 2008. Through October 2008, approximately 300 patients

have been treated. Assuming 80 seeds are used per patient that equals approximately 24,000 seeds that have been implanted through October 2008. At approximately $30.00/seed, sales of approximately $0.72 million have been achieved through October 2008. Sales are expected to exceed $1 million by January 2009. A bar graph showing sales from March 2008 through October 2008 was enclosed with the Amendment and Response filed on March 9, 2009. Total sales for 2009 were an estimated two million dollars.

Applicant has shown objective evidence of long-felt but unmet need and commercial success. Accordingly, claims 36-46 and 48-70 are not obvious over Zamora in view of Slater, Stinson, and Reed.

Double Patenting Rejection

Claims 36-40, 45, and 47-55 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 10, 12, 13, 30, 32, 35, 38, and 41 of U.S. Patent No. 6,746,661 to Kaplan. Applicants respectfully traverse this rejection.

The mere fact that claims are drawn to brachytherapy seeds, formed of a biodegradable polymer, but having distinct limitations - one drawn to elastic properties of the polymer and the other to distinct structures for maintaining the location of the seed, does not make them obvious over the other. If they had appeared in the same application, the Examiner likely would have issued a restriction requirement on the grounds that they required different searches, in different

arts. Elastic polymers do not make obvious structures for maintaining seeds in a particular location.

The Examiner states that "the polymers used in the instant claims and the polymers disclosed in U.S. 6,746,661 are biodegradable polymers and would have elastic properties. The instant claims are within the scope of the claims of the '661 patent. Thus, scope is overlapping each other and properly included in the rejection because they are patentably distinct from each other." The Examiner is clearly applying the wrong legal standard.

In determining whether a nonstatutory basis exists for a obviousness-type double patenting rejection, the first question to be asked is - does any claim in the application define an invention that is an obvious variation of an invention claimed in the patent? See *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 USPQ2d 1869 (Fed. Cir. 2001); *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000). Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis.

The Examiner has failed to do the analysis described above. The Examiner's conclusion that the polymer in the instant claims and the claims of the '661 patent is biodegradable and would have elastic properties is unclear. There is no relationship between biodegradability and elasticity. For Example, poly-3-hydroxybutyrate (PHB) and polylactic acid (PLA) are

biodegradable polymers, however, they are typically classified as stiff and brittle. Moreover, the fact that the instant claims and the claims of the '661 patent include biodegradable polymers is irrelevant. The question is whether the seeds of the instant claims are obvious in view of the claims of the '661 patent.

The claims of the '661 patent describe a brachytherapy seed comprising a plurality of microspheres comprising a biocompatible component, one or more therapeutic active agents, and a radiopaque marker, wherein the seed has a size and shape suitable for passing through the bore of a needle having an interior diameter of less than 2.7 mm. In contrast, the pending claims do not require a plurality of microspheres and further require one or more biodegradable structures for maintaining the location or orientation of the seed, let alone the specific structures in claim 36. The claims of the '661 patent do not disclose or suggest one or more biodegradable structures for maintaining the location or orientation of the seed. The Examiner has failed to point to any claim in the '661 patent that discloses or suggest such structures. Accordingly, claims 36-40, 45, and 47-55 are not obvious over the claims in U.S. Patent No. 6,747,661 to Kaplan, *et al.* Therefore, this rejection should be withdrawn.

Allowance of claims 36-46 and 48-70, as amended and new claims 71-79 is respectfully solicited.

Respectfully submitted,

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